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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,492	02/12/2001	Charles Nicolette	20363-004 (DFCI-4)	7050

7590 07/29/2002

Ivor R. Elrifi, Esq
MINTZ, LEVIN, COHN, FERRIS,
GLOVSKY and POPEO, P.C.
One Financial Center
Boston, MA 02111

EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/782,492	Applicant(s) NICOLETTE ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *1-31,56-83 and 86-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-55,84 and 85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group III, claims 32-55, 84, and 85 in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-88 are pending, however, claims 1-31, 56-83, and 86-88 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

Claims 32-55, 84, and 85 are under current examination.

Priority

It is acknowledged that this application claims the benefit of priority to U.S. provisional application 60/043,609, filed April 15, 1997.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-55, 84, and 85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are vague and indefinite because of the claim recitation "at the expense", the specification fails to define the term, it is unclear the meaning of the term in the context of the claims.

Claims 34 and 44 are vague and indefinite because of the claim recitation, "the cells". The base claims 33 and 42 recite at least two types of cells, e.g. immune effector cells and hybrid cells, it is unclear which type of cell they refer to.

Claim 52 is vague and indefinite because of the claim limitation "naïve". Claim 52 depends from claim 42, drawn to a population of educated, antigen-specific immune effector cells. The specification defines the term "educated" immune effector cells as cells that have interacted with an antigen such that they differentiated into an antigen-specific cell (page 9, line 30). Thus, it is unclear how the educated cells are also naïve, the metes and bounds of the claims are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-55, 84, and 85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the educated immune effector cells as a vaccine in a mouse tumor model, does not reasonably provide enablement for using such as a vaccine in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

Claims 84 and 85 are directed to a vaccine comprising the population of antigen-specific immune effector cells of claims 32 or 42. These claims clearly or implicitly state the intended use of the composition and methods. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c) When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. "A vaccine composition" is defined as a composition for therapeutic use, to prevent, alleviate, treat, or cure a disease within the animal to which the substance is administered, therefore, will be evaluated by that standard.

In view of the guidance provided, the specification teaches that the fusion cells could generate CTLs when co-cultured with patient PBMC to have low levels of lyses of autologous ovarian cancer cells, and reversed tolerance to MUC1 tumor cells in MUC1

transgenic mice. However, the specification fails to teach whether such vaccine effect could be achieved in other animals, particularly in humans.

In view of the state of the art and levels of the skill in the art of cancer immunotherapy, the applicants' attention is directed to the teachings of *Bodey et al,* and *Radoja et al*, which teach that although the mouse model has served as a useful tool for study cancer therapy, the artificially established tumor differs from the naturally occurring cancer in humans. *Bodey et al* (Anticancer Res 2000;20:2665-76) review cancer vaccines in cancer immunotherapy, "THE THEORETICAL BASIS FOR ALL OF THESE APPROACHES IS VERY WELL FOUNDED. ANIMAL MODELS, ALBEIT HIGHLY ARTIFICIAL, HAVE YIELDED PROMISING RESULTS. CLINICAL TRIALS IN HUMANS, HOWEVER, HAVE BEEN SOMEWHAT DISAPPOINTING...", "THE CANCER VACCINE APPROACH TO THERAPY IS BASED ON THE NOTION THAT THE IMMUNE SYSTEM COULD POSSIBLY MOUNT A REJECTION STRENGTH RESPONSE AGAINST THE NEOPLASTICALLY TRANSFORMED CELL CONGLOMERATE. HOWEVER, DUE TO THE LOW IMMUNOGENICITY OF TUMOR ASSOCIATED ANTIGENS, DOWNREGULATION OF MHC MOLECULES, THE LACK OF ADEQUATE COSTIMULATORY MOLECULE EXPRESSION, SECRETION OF IMMUNE INHIBITORY CYTOKINES, ETC., SUCH EXPECTATION ARE RARELY FULFILLED...FAULTY ANTIGEN PRESENTATION WHICH COULD RESULT IN TOLERANCE INDUCTION TO THE ANTIGENS CONTAINED WITHIN THE VACCINE, AND SUBSEQUENT RAPID TUMOR PROGRESSION." (page 2665, column one). *Radoja et al* (Mol Med 2000;6:465-79) teach that cancer-induced defective cytotoxic T lymphocyte is probably another mechanism how tumor antigen escape immune surveillance. "THE NOTION THAT A DEFICIT IN IMMUNE CELL FUNCTIONS PERMITS TUMOR GROWTH HAS RECEIVED EXPERIMENTAL SUPPORT WITH THE DISCOVERY OF SEVERAL DIFFERENT BIOCHEMICAL DEFECTS IN T LYMPHOCYTES THAT INFILTRATE CANCERS" (abstract). "ACCUMULATION OF CIRCULATING

ANTITUMOR IMMUNOGLOBULIN G IN CANCER PATIENTS SHOW THAT THE PRIMING PHASE OF ANTITUMOR IMMUNE RESPONSE IS FUNCTIONAL DURING THE RELATIVELY SLOW PROCESS OF NASCENT TUMOR GROWTH...IN BOTH HUMAN CANCER PATIENTS AND RODENTS BEARING TUMORS OF DIFFERENT HISTOLOGIC ORIGIN, SYSTEMIC IMMUNITY IS NOT PROFOUNDLY SUPPRESSED..." "HOWEVER, INHIBITION OF A SPECIFIC ANTITUMOR IMMUNE RESPONSE HAS BEEN OBSERVED FREQUENTLY. A VARIETY OF MECHANISM HAVE BEEN PROPOSED TO ACCOUNT FOR DEFECTIVE ANTITUMOR IMMUNE RESPONSE, INCLUDING: SECRETION OF SUPPRESSIVE FACTORS IN THE TUMOR MICROENVIRONMENT, THE LACK OF EXPRESSION OF COSTIMULATORY SIGNALS ON TUMOR CELLS, INDUCTION OF REGULATORY T CELLS HAVING A SUPPRESSIVE PHENOTYPE, LOSS OF ANTIGEN PRESENTATION FUNCTION IN THE TUMOR, LOSS OF EXPRESSION OF HLA CLASS I ANTIGEN PRESENTING MOLECULES IN TUMORS, TUMOR-INDUCED T-CELL SIGNALING DEFECTS, LOSS OF TUMOR ANTIGEN EXPRESSION, IMMUNOLOGICAL IGNORANCE AND, SINCE MANY TUMOR ANTIGENS ARE EITHER UNMODIFIED SELF OR EPITOPES CLOSELY RELATED TO SELF, THE REDUCTION OF THE REPERTOIRE OF POTENTIAL HIGH AFFINITY ANTITUMOR T-CELL CLONES DURING T-CELL MATURATION IN THE THYMUS" (Introduction).

Long after the effective filing date of the instant application, *Moingeon et al* (Trends Immunol 2002 Apr;23:173-5) teach, "THE NEED FOR ANTIGEN-PRESENTATION PLATFORMS AND/OR ANTIGEN FORMULATIONS ELICITING POTENT T-CELL RESPONSES AND MUCOSAL IMMUNITY IN HUMANS, AS WELL AS THE POOR PREDICTIVE VALUE OF ANIMAL MODELS, WERE EMPHASIZED ALSO". (paragraph bridging pages 174 and 175)

Thus, it is evident that at the time of the invention, the skilled artisan in the relevant art, while acknowledging the significant potential of immunotherapy for cancer, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon

applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides ex vivo and in vivo data in a mouse tumor model to illustrate a potential therapeutic use of the claimed compositions, it is not enabled for its full scope because the art-recognized barriers in achieving successful cancer immunotherapy and differences in immune responses between a mouse tumor model and cancer patients. The instant specification does not provide any *in vivo* data to show that the instant invention has overcome the deficiency present in the pre- and post-filling art. Thus, it would require undue experimentation for any person skilled in the art to practice the instant invention in humans.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* cancer immunotherapy in humans, the lack of direction or guidance provided by the specification as well as the breadth of the claims directed to the use of numerous immune effector cells in cancer patients, it would have required undue experimentation for one skilled in the art to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 32, 35, 42, 45, 84, and 85 are rejected under 35 U.S.C. 102(e) as being anticipated by *Nair et al* (US 6,306,388).

These claims are directed to a substantially pure population of educated, antigen-specific immune effector cells expanded in culture, wherein the cells are cytotoxic T lymphocytes and recognizing tumor-specific antigen, and a composition comprising the immune effector cells and a pharmaceutically acceptable carrier.

Nair et al teach a population of CTL educated by tumor-specific antigen presenting cells, and the CTL could be administered to a patient in a method of adoptive immunotherapy (see abstract for example). Therefore, *Nair et al* anticipate instant claims.

Please note that claim recitations "at the expense of hybrid cells", "produced by culturing immune effector cells with hybrid cells" have not given patentable weight in this and following rejection, because patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

Claims 32, 35, 42, 45, 84, and 85 are rejected under 35 U.S.C. 102(e) as being anticipated by *Granucci et al* (6,156,307).

Granucci et al teach production of a population of activated T-lymphocytes by co-culturing of naïve or antigen-specific T lymphocytes with the antigen-loaded dendritic cell line, and then use the activated T cells for generating desired immune response in vivo, wherein the antigens include tumor, or pathogens (paragraph bridging columns 4 & 5), wherein the antigen-loading encompasses transferring genes coding for antigenic determinants to DCs (column 5, lines 19-26), wherein the DCs could be further modified by other genes such as cytokine genes for modulating the immune response (column 5, lines 43-48). Therefore, *Granucci et al* anticipate instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32-55, 84, and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Granucci et al* (6,156,307) as applied to claims 32, 35, 42, 45, 84, and 85 above, and in view of *Moser et al* (WO96/30030, PTO-1449/B1).

Granucci et al teach producing the CTLs with genetically modified dendritic cells, not hybrid cells.

Moser et al teach hybrid cells between dendritic cells from autologous or allogeneic HLA-matched dendritic cells fused with autologous tumor cells, which could be used for conferring tumor resistance *in vivo* (see abstract), or for *in vitro* activation of

autologous immune cells into anti-tumor immune effectors in the presence of IL-2 (educated, antigen-specific CTLs, page 17, lines 15-21, and page 19, lines 9-19). *Moser et al* go on to teach the advantage of using somatic cell fusion in cancer therapy, such as brings together the known and unknown tumor antigens, co-stimulating factors and transposable to human cancer patients (paragraph bridging pages 5 and 6). *Moser et al* do not teach genetic modification of the hybrid cells.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the fused cells of *Moser et al* in the process of *Granucci and Moser et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so because of the substantial advantages using the fused cells over using dendritic cell alone as taught by *Moser et al*, yet the fused cells still could be used for genetic modification to obtain certain desired features as taught by *Granucci et al* for enhanced activation of CTLs. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
July 16, 2002

JAMES KETTER
PRIMARY EXAMINER